Remarks

Claims 1-20 were pending. Applicants have canceled claims 2-5, 7, and 9-18 without prejudice to Applicants' right to pursue their subject matter in the present application and in related applications.

Applicants have amended claim 1 to delete unnecessary words and to recite a method of detecting or monitoring lupus in a subject, the method comprising the steps of detecting an SFRP1 expression profile in a kidney sample of a subject; comparing said SFRP1 expression profile to a reference SFRP1 expression profile; and using said comparison to detect or monitor lupus in said subject, wherein said subject is a mouse or human. Support for the amendments to claim 1 is found in the original application at least in Table 1; in paragraphs **[0014] – [0018]**, **[0050] – [0054]**, **[0072] – [0073]**, and **[0200] – [0201]**; and in original claims 1, 4, 6, 7, and 9.

Applicants have amended claims 6 and 8 to depend from claim 1.

Applicants have amended claim 19 to delete unnecessary words and to recite a method comprising contacting lupus-affected or lupus-predisposed mouse kidney cells with an agent; and comparing expression of SFRP1 in said mouse kidney cells before and after said contacting to determine if said agent modulates SFRP1 expression. Applicants have amended claim 20 to delete unnecessary words and to recite a method comprising: administering an agent to a lupus-affected or lupus-predisposed mouse; and comparing expression of SFRP1 in kidney samples of the mouse before and after said administering to determine if said agent modulates expression of SFRP1 in the mouse. Support for the amendments to claims 19 and 20 is found in the original application at least in Table 1; in paragraphs **[0016]**, **[0025] – [0026]**, **[0050] – [0054]**, **[0072]**, **[0077]**, and **[0202] – [0203]**; and in original claims 4, 19 and 20.

Applicants submit that the present amendments introduce no new matter into the present application. Upon entry of the present amendment, claims 1, 6, 8, 19 and 20 will be pending and presented for consideration.

Enablement rejections under 35 U.S.C. § 112

The Office action rejected claims 1-4, 6-9, 19 and 20 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office action acknowledged that the specification enables methods for determining an expression profile in a mouse wherein the methods comprise obtaining a kidney sample from a control, LN-free mouse and a test mouse; determining the level of "SFRP1 (SEQ ID NO:15)" mRNA in the control LN-free mouse and in the test mouse; comparing the level of "SFRP1 (SEQ ID NO:15)" mRNA in the control LN-free mouse and in the test mouse; and determining that the test mouse has an increased likelihood of having LN if the test mouse has an increase in "SFRP1 (SEQ ID NO:15)" mRNA as compared to the control, LN-free mouse. The Office action also acknowedged that the specification enables methods comprising contacting an LN-affected or LN-predisposed mouse kidney cell or mouse with a test agent; determining the level of "SFRP1 (SEQ ID NO:15)" mRNA in said kidney cell or in a kidney cell of said mouse; comparing the level of "SFRP1 (SEQ ID NO:15)" mRNA in said kidney cell or in said kidney cell of said mouse after said contacting to the level of "SFRP1 (SEQ ID NO:15)" mRNA prior to said contacting; and determining that said agent modulates mRNA expression in said kidney cell or said kidney cell of said mouse if there is a decrease in the level of "SFRP1 (SEQ ID NO:15)" mRNA after said contacting step as compared to prior to said contacting step. The Office action nevertheless argues that the claims do not bear a reasonable correlation to the scope of enablement, alleging specifically that the specification 1) does not teach an association between the expression of SFRP1 in a representative number of additional organisms or cell or tissue types; 2) does not teach a representative number of genes that are differentially expresssed in pre-symptomatic lupus-affected or -predisposed tissues as compared to disease-free tissues; and 3) does not teach a representative number of autoimmune diseases which could be detected or monitored.

Applicants request reconsideration and withdrawal of the rejections.

Independent claim 1

Applicants have amended claim 1 to recite a method of detecting or monitoring lupus in a mouse or human comprising detecting an SFRP1 expression profile in a kidney sample. Applicants submit that by reciting "a kidney sample," Applicants have addressed the concern

regarding the representative number of cell or tissue types, as the application demonstrates the usefulness of kidney samples. Applicants submit that by reciting "SFRP1," Applicants have addressed the concern regarding the representative number of genes that are differentially expressed in pre-symptomatic lupus-affected or -predisposed tissues as compared to disease-free tissues. Applicants submit that by reciting "lupus," Applicants have addressed the concern regarding the representative number of autoimmune diseases which could be detected or monitored.

Applicants have amended claim 1 to recite "mouse or human." Applicants submit that in view of the enablement and working example with respect to mice in the application and the specific guidance in the application relating to the corresponding human gene and methods of its detection, the specification enables a representative number of organisms for a claim reciting "mouse or human." Applicants understand that the Office action argues that gene expression patterns are not completely predictable among different organisms. The Office action cites two post-filing references to emphasize its position. The "Liu" reference (Liu *et al.* (2004) Clin. Immunol. 112:225-230) indicates that a mouse model for lupus different from the one used in the present application does not "perfectly model" the corresponding human disease "at least in the perspective of gene expression profile." Applicants note that, under M.P.E.P. § 2164.05(a): "In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling." While M.P.E.P. § 2164.05(a) acknowledges certain exceptions, such as where the reference evidences what would have been known on the filing date; where the reference states that the invention is not possible; or where the reference evidences what one of skill in the art would have believed to be predictable on the filing date, arguably none of these exceptions is applicable here. Even if Liu cautions that not some mouse models are not perfect models, Liu does not demonstrate the inoperability of the present invention and does not indicate that the mouse model used in the present application is somehow deficient or that the mouse model used in the present application was believed (as of the effective filing date) unlikely to be applicable to human disease.

Indeed, the conclusion to be drawn from the "Coleman" reference (Coleman (2003) Drug Discovery Today 8(6):233-235) is to the contrary. According to the Office action, Coleman concludes that "the validity of mouse or other animal species as a human surrogate should not be

assumed." This quotation from Coleman, however, is preceded by the following two sentences of Coleman's conclusory paragraph: "Unsurprisingly, the results demonstrated that many, but not all, gene expression patterns of human and mouse are similar. Therefore, if an experimental model is needed as a predictor of human biology and disease, the mouse is useful." Thus, Coleman finds a certain degree of predictability in comparisons of human and mouse gene expression patterns, even if the patterns are not identical. More importantly, Coleman was *unsurprised* by this predictability, likely evidencing the expectation of one of ordinary skill in the art as of the February 2003 effective filing date of this application.

The enablement requirement requires no more than a reasonable correlation between the scope of the claims and the scope of enablement provided by the specification. It does not require working examples of all embodiments of the invention, nor does it require perfect predictability. It requires no more than teachings permitting one of ordinary skill in the art to practice the claimed invention without undue experimentation. Applicants submit that in view of the amendments to claim 1, the resulting scope of the claim, the teachings in the specification including the working example with respect to mice and the guidance with respect to humans, the unsurprising similarity of "many, but not all, gene expression patterns of human and mouse," the high level of skill in the art, and the routine nature of the experimentation involved, there is a reasonable correlation between the scope of the claims and the scope of enablement provided by the specification.

Applicants also note that the USPTO has made clear in the context of the utility requirement that "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials" (MPEP § 2107.03(IV)).

Applicants therefore request reconsideration and withdrawal of the rejection of claim 1 and of all claims depending therefrom.

Independent claims 19 and 20

Applicants have amended claims 19 and 20 to recite "mouse," "kidney cells" (claim 19) or "kidney samples" (claim 20), "SFRP1" and "lupus." Accordingly, Applicants believe the amendments to claims 19 and 20 address each of the concerns raised in the Office action regarding the scope of enablement of the claims. Applicants believe the scope of claims 19 and

20 bear a reasonable correlation with the scope of enablement provided by the specification and request reconsideration and withdrawal of the rejection of claims 19 and 20.

Written description rejections under 35 U.S.C. § 112

The Office action rejected claims 1-3, 6-9, 19 and 20 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Office action alleged that the information provided in the specification does not reasonably convey possession of the claimed genus of *any* gene differentially expressed in *any* predisposed or presymptomatic lupus-affected tissue. The Office action did acknowledge, however, that "methods for detecting the SFRP1 gene of SEQ ID NO:15 meet the written description requirement."

Applicants have amended the claims to recite the detection of SFRP1 in mouse or human kidney cells or samples. Although the claims do not recite "SEQ ID NO:15," Applicants submit that it is clear from the specification (see, *e.g.*, paragraphs **[0034]** and **[0072]**) that one would detect the mouse SFRP1 gene in mouse cells or samples and would detect the human SFRP1 gene in human mouse cells or samples. The mouse and human SFRP1 genes were known and characterized at the time of the present application. Accordingly, naming the SFRP1 gene provides a sufficiently detailed, relevant identifying characteristic to evidence that Applicants were in possession of the claimed invention. Applicants point the Examiner to Capon v. Eshar as quoted in M.P.E.P. § 2163: "'The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes' where the genes were novel combinations of known DNA segments." Here, Applicants claim novel methods using known genes. The amended claims therefore fully comport with the written description requirement and Applicants request reconsideration and withdrawal of the rejections.

Rejections under 35 U.S.C. § 112, second paragraph

The Office action rejected claims 1-4, 6-9, 19 and 20 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite over recitations of "lupus-affected," "early-stage lupus affected," "predisposed tissues, "disease-free tissues," "disease-free kidney tissues," and

"wherein at least one gene is differentially expressed in early-stage lupus as compared to disease-free tissues."

Applicants request reconsideration and withdrawal of these rejections.

As amended, none of claims 1-4 or 6-9 recite "lupus-affected," "early-stage lupus affected," "predisposed tissues, "disease-free tissues," "disease-free kidney tissues," or "wherein at least one gene is differentially expressed in early-stage lupus as compared to disease-free tissues." Applicants submit that claims 1-4 and 6-9 are definite and request reconsideration and withdrawal of the rejections.

As amended, claim 19 recites "lupus-affected or lupus-predisposed mouse kidney cells," but contains none of the other recitations that prompted the rejection under 35 U.S.C. § 112, second paragraph. At page 19, the Office action states: "Regarding 'predisposed tissues,' it is unclear as to what the tissues are predisposed . . . *e.g.* lupus." Applicants submit that, as amended, the term "lupus-predisposed" is definite. At page 19, the Office action also states that: "It is further unclear as to whether a predisposed tissue is any tissue from a subject predisposed to developing lupus . . . or if a predisposed tissue is any tissue that would be affected by lupus, *e.g.* a kidney tissue." Applicants submit that "lupus-predisposed mouse kidney cells" is definite. The Office action also alleges that "it is unclear as whether lupus-affected . . . tissues include any tissues obtained from a subject having lupus . . . ." Again, Applicants submit that as amended, "lupus-affected or lupus-predisposed mouse kidney cells" is clear and definite. Applicants accordingly request reconsideration and withdrawal of the rejection of claim 19.

Applicants submit that the recitation of "a lupus-affected or lupus-predisposed mouse" in amended claim 20 is equally definite and Applicants request reconsideration and withdrawal of the rejection of claim 20.

Provisional double patenting rejections

The Office action provisionally rejected claims 1-3, 6-9 and 19-20 as allegedly unpatentable over claims 1-3, 5-8 and 22 of U.S. application 10/686,619 under the judicially-created doctrine of obviousness-type double patenting. Applicants have amended each of the pending independent claims in the present application to recite SFRP1. The recited claims of

U.S. application 10/686,619 do not relate to SFRP1. Applicants submit that the present claims are not obvious in view of the claims of U.S. application 10/686,619. Applicants therefore request reconsideration and withdrawal of the rejections.

Rejections under 35 U.S.C. § 102

The Office action rejected claims 1-4 and 6-9 under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,706,867 ("Lorenz"). The Office action rejected claims 1-4, 6, 7 and 9 under 35 U.S.C. § 102(b) as allegedly anticipated by Ugolini *et al.* (2001) Oncogene 20:5810-5817 ("Ugolini"). The Office action rejected claims 1-3, 6, 7, 9 and 19 under 35 U.S.C. § 102(b) as allegedly anticipated by Rider *et al.* (1998) Clin. Immunol. Immunopathol. 89(2):171-180 ("Rider"). The Office action rejected claims 1-4 and 6-9 under 35 U.S.C. § 102(a) as allegedly anticipated by Ijiri *et al.* (2002) J. Rheumatol. 29(11):2266-2270 ("Ijiri").

Applicants request reconsideration and withdrawal of these rejections.

Applicants have amended claim 1 to recite a method of detecting or monitoring lupus comprising detecting an SFRP1 expression profile. None of Lorenz, Ugolini, Rider, or Ijiri teaches a method of detecting or monitoring lupus comprising detecting SFRP1. Accordingly, none of Lorenz, Ugolini, Rider or Ijiri anticipates claim 1 or any claim depending therefrom. Applicants have amended claim 19 to recite comparing expression of SFRP1 in mouse kidney cells. Rider does not teach comparing expression of SFRP1 in mouse kidney cells. Applicants therefore respectfully request reconsideration and withdrawal of all rejections under 35 U.S.C. § 102.

Rejections under 35 U.S.C. § 103

The Office action rejected claim 8 under 35 U.S.C. § 103 as allegedly unpatentable over Ugolini in view of Lorenz. The Office action rejected claims 8 and 20 under 35 U.S.C. § 103 as allegedly unpatentable over Rider in view of Lorenz.

Applicants request reconsideration and withdrawal of these rejections.

Claim 8 depends from claim 1 and incorporates its limitations. As amended, claim 1 relates to a method comprising using a comparison of SFRP1 expression profiles to detect or monitor lupus. None of Ugolini, Lorenz or Rider teaches using a comparison of SFRP1

expression profiles to detect or monitor lupus. None of Ugolini, Lorenz or Rider provides a specific motivation to use a comparison of SFRP1 expression profiles to detect or monitor lupus. None of Ugolini, Lorenz or Rider provides a reasonable expectation of success in using a comparison of SFRP1 expression profiles to detect or monitor lupus. Accordingly, separately or in combination, Ugolini, Lorenz and Rider fail to render obvious the invention of claim 8.

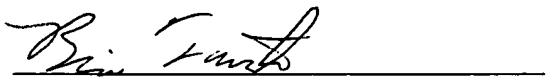
As amended, claim 20 relates to a method comprising administering an agent to a lupus-affected or lupus-predisposed mouse and comparing expression of SFRP1 in kidney samples of the mouse before and after administration of the agent. Neither Lorenz nor Rider relates to detection of SFRP1 in a lupus-affected or lupus-predisposed mouse, as neither reference connects SFRP1 and lupus. Accordingly, the references fail to provide any motivation for practicing the claimed invention.

Applicants therefore request reconsideration and withdrawal of all rejections under 35 U.S.C. § 103.

CONCLUSION

Upon entry of the present amendment, claims 1, 6, 8, 19 and 20 will be pending and presented for consideration. Examiner Myers is encouraged to telephone the undersigned attorney to discuss any remaining issues.

Respectfully submitted,



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Reg. No. 48,645

Brian Fairchild, Ph.D.
Attorney for Applicants
Kirkpatrick & Lockhart Nicholson Graham LLP
State Street Financial Center
One Lincoln Street
Boston, Massachusetts 02111-2950

Tel. No.: (617) 261-3169
Fax No.: (617) 261-3175